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(54) Titre : COMPRIME A CROQUER CONTENANT DE LA LYSINE
(54) Title: CHEWABLE TABLET CONTAINING LYSINE

(57) Abrégé/Abstract:
The invention relates to a chewable tablet with enhanced compliance by humans, in particular children and/or juveniles comprising at least one vitamin, optionally at least one mineral, lysine or a pharmaceutically acceptable salt thereof, at least one sweetener having the capability of masking the disgusting flavor of lysine, optionally one flavoring agent and a pharmaceutically or dietetically acceptable carrier.

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(54) Title: CHEWABLE TABLET CONTAINING LYSINE

(57) Abstract: The invention relates to a chewable tablet with enhanced compliance by humans, in particular children and/or juveniles comprising at least one vitamin, optionally at least one mineral, lysine or a pharmaceutically acceptable salt thereof, at least one sweetener having the capability of masking the disgusting flavor of lysine, optionally one flavoring agent and a pharmaceutically or dietetically acceptable carrier.

CHEWABLE TABLET CONTAINING LYSINE

FIELD OF THE INVENTION

The present invention relates to a tablet with enhanced compliance by humans, in particular children and/or juveniles comprising at least one vitamin, optionally at least one mineral and lysine or a pharmaceutically acceptable salt thereof.

BACKGROUND OF THE INVENTION

It is known that lysine as an essential amino acid enhances appetite and, together with Vitamin D3, improves the absorption of Calcium. The prior art dealing with lysine as nutritional supplement may be best illustrated by the following references:
Albanese A.A. et al., NY State J. Med. 1955; 55, 3453-3456 describe lysine supplementation in infant feeding. Graham G.G. et al., Am. J. Clin. Nutr. 1969; 22 (11), 1459-1468 describe the effect of lysine enrichment of wheat flour for the evaluation in infants. Civitelli R. et al., Nutrition 1992; 8 (6), 400-405, disclose the metabolism of (L)-lysine and calcium in humans. Fürst P., Nutrition 1993; 9 (1), 71-72 suggests (L)-lysine as a nutritional tool in the prophylaxis and treatment of osteoporosis. Flodin N. W., J. Am. Coll. Nutr. 1997; 16 (1), 7-21, reviews the metabolic roles, the pharmacology and the toxicology of lysine.

Accordingly, there is a need to provide humans, in particular children and/or juveniles with lysine supplementation. However, children will hardly accept chewable tablets which contain effective amounts of lysine due to its disgusting taste. The problem underlying the present invention was to provide a lysine containing chewable tablet which is well accepted by children and/or juveniles.

SUMMARY OF THE INVENTION

The invention relates to a tablet with enhanced compliance by humans comprising the following constituents:

(a) at least one vitamin,

(b) optionally at least one mineral,

(c) lysine or a pharmaceutically acceptable salt thereof,

(d) at least one sweetener and optionally at least one flavoring agent having the capability of masking the disgusting flavor of lysine,

(e) and a pharmaceutically or dietetically acceptable carrier.

In an embodiment, there is provided a tablet with enhanced compliance by humans comprising the following constituents: a) at least one vitamin, (b) at least one mineral which is manganese (II) gluconate, copper (II) carbonate, calcium phosphate, ferrous (II) fumarate, zinc oxide or magnesium oxide, (c) lysine or a pharmaceutically acceptable salt thereof, (d) at least one sweetener and optionally at least one flavoring agent having the capability of masking the disgusting flavor of lysine, (e) and a pharmaceutically or dietetically acceptable carrier, wherein said tablet is obtainable by mixing of the different components (a) to (e) and tabletting by direct compression.

Another aspect of the present invention is a method of improving the physiological state of humans which method comprises administering an effective amount of the tablet according to the present invention.

Furthermore, the invention relates to a method for the manufacture of a tablet according to the present invention which method comprises mixing of the different components (a) to (e) and tabletting by direct compression.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates in particular to tablets to be sucked or chewed by children and/or juveniles wherein the disgusting taste caused by lysine is masked.

Specifically the subject matter of this invention provides tablets intended for the oral way, to be sucked or to be chewed, containing as active ingredients lysine, one or more vitamins and optionally one or more minerals. Lysine is preferably provided in form of a pharmaceutically acceptable salt, in particular as (L)-lysine monohydrochloride. Most preferably the tablet comprises 10 to 100 mg, in particular about 50 mg of (L)-lysine monohydrochloride per unit dosage.

Preferably component (a) comprises at least one vitamin selected from the group consisting of retinol equivalents such as β-carotene or vitamin A, vitamin B such as vitamin B1, vitamin B2, vitamin B6 or vitamin B12, vitamin C, vitamin D such as vitamin D3, vitamin E, folic acid, vitamin H and vitamin PP.

The ranges of amounts of ingredients given hereinabove and hereinbelow relate to the declared amount of said ingredients and include appropriate stability overdosages.

Most preferably component (a) is a mixture of vitamins consisting essentially of 0.4 to 0.8 mg, in particular about 0.5 to 0.7 mg of β-carotene, 500-1500 IU , in particular about 700-1100 IU of vitamin A palmitate, 0.3 to 1.0 mg, in particular about 0.4 to 0.6 mg of vitamin B1 nitrate, 0.3 to 1.0 mg, in particular about 0.5 to 0.7 mg of vitamin B2, 0.3 to 1.0 mg, in

particular about 0.5 to 0.7 mg of vitamin B6 hydrochloride, 0.4 to 1.0 µg, in particular about 0.5 to 0.9 µg of vitamin B12, 15 to 40 mg, in particular about 20 to 30 mg of vitamin C, 100-300 IU, in particular about 125-200 IU of vitamin D3, 3.0 to 9.5 mg, in particular about 4.0 to 6.5 mg of vitamin E acetate, 20 to 80 µg, in particular about 40 to 70 µg of folic acid, 10 to 25 µg, in particular about 14 to 21 µg of vitamin H and 4 to 10 mg, in particular about 5 to 8 mg of vitamin PP per unit dosage.

Preferably component (b) comprises at least one mineral selected from the group consisting of manganese such as manganese (II) gluconate, copper such as copper (II) carbonate, calcium such as dicalcium phosphate anhydrous, iron such as ferrous (II) fumarate, zinc such as zinc oxide and magnesium such as magnesium oxide.

Most preferably component (b) is a mixture consisting essentially of 0.2 to 0.8 mg, in particular about 0.4 to 0.6 mg of copper (II) carbonate, 150 to 300 mg, in particular about 200 to 250 mg of dicalcium phosphate anhydrous, 8 to 20 mg, in particular about 11 to 14 mg of ferrous (II) fumarate, 4 to 9 mg, in particular about 6 to 7 mg of zinc oxide and 12 to 28 mg, in particular about 18 to 21 mg of magnesium oxide per unit dosage.

Preferably component (d) contains at least one sweetener selected from the group consisting of calcium saccharinate, ammonium cyclamate, ammonium glycirhizinate, Aspartame (N-*L*-α-aspartyl-*L*-phenylalanine 1-methylester), glucose and glucitols such as inositol, mannitol, sorbitol or dulcitol and at least one flavouring agent selected from the group consisting of natural citrus or orange flavour and Prosweet®, which is a commercially available natural flavouring.

Most preferably component (d) consists essentially of 1.0 to 10.0 mg, in particular 4.0 to 8.0 mg of Aspartame, 100.0 to 400.0 mg, in particular 200.0 to 350.0 mg of glucose, 200 to 800 mg, in particular 300 to 700 mg of sorbitol, 5.0 to 50.0 mg, in particular 10.0 to 30.0 mg of natural orange flavour and 1.0 to 10.0 mg, in particular 2.0 to 6.0 mg of Prosweet® per unit dosage.

Preferably component (e) comprises at least one carrier selected from the group consisting of diluents, excipients, sticking agents, bulk agents, preservatives, colorants and other pharmaceutical or food processing agents.

Among the suitable excipients or diluents, it may particularly be cited acidifying or buffering agents such as citric acid, urea or glycine, bulk agents such or mannitol or sorbitol, adhering agents with low speed of dissolution such as alkyl cellulose, for example methyl cellulose, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose or carboxy methyl cellulose or copolymers of methacrylic and acrylic acid; binding agents such as silicon dioxide, polyvinyl pyrrolidone, arabic gum, guar gum, adraganth gum, karaya gum, lubricating agents such as magnesium stearate, inert diluents such as lactose, gelatin, starch, mono- or diglyceride fatty acids, edible fatt, sodium aluminium silicate, hydrogenated vegetable oil, calcium carbonate, magnesium phosphate or calcium sulphate; skim milk powder, sodium caseinate.

Among the suitable colorants, it may particularly be cited Turmeric powder (E100), Carmine powder (E120), beta-carotene and Sunset Yellow (E110), Beetroot Red (E162), Erythrosine Red (E127), or a combination of these colorants.

Most preferred is a tablet which can be chewed or sucked with enhanced compliance by children and/or juveniles, preferably at an age of 4 to 16, in particular 6 to 14 years comprising the following constituents:

(a) a mixture of vitamins consisting essentially of 0.4 to 0.8 mg of β-carotene, 500-1500 IU of vitamin A palmitate, 0.3 to 1.0 mg of vitamin B1 nitrate, 0.3 to 1.0 mg of vitamin B2, 0.3 to 1.0 mg of vitamin B6 hydrochloride, 0.4 to 1.0 µg of vitamin B12, 15 to 40 mg of vitamin C, 100-300 IU of vitamin D3, 3.0 to 9.5 mg of vitamin E acetate, 20 to 80 µg of folic acid, 10 to 25 µg of vitamin H and 4 to 10 mg of vitamin PP per unit dosage,

(b) a mixture of minerals consisting essentially of 0.2 to 0.8 mg of copper (II) carbonate, 150 to 300 mg of dicalcium phosphate anhydrous, 8.0 to 20 mg of ferrous (II) fumarate, 4 to 9 mg of zinc oxide and 12-28 mg of magnesium oxide per unit dosage,

(c) 10 to 100 mg of (L)-lysine monohydrochloride per unit dosage,

(d) a mixture of sweeteners and flavoring agents consisting essentially of 1.0 to 10.0 mg of Aspartame, 5.0 to 50.0 mg of glucose syrup, 200 to 800 mg of sorbitol, 5.0 to 50.0 mg of natural orange flavour and 1.0 to 10.0 mg of Prosweet® per unit dosage;

(e) a pharmaceutically or dietetically acceptable carrier,

wherein the complete dosage unit weighs 500 to 2000 mg.

Another aspect of the present invention resides in a method of improving the physiological state of humans, in particular improving the development and growth of children and/or juveniles, most preferably at an age of 4 to 16 years comprising administering orally an effective amount of a tablet comprising the following constituents to said humans:

(a) at least one vitamin,

(b) optionally at least one mineral,

(c) lysine or a pharmaceutically acceptable salt thereof,

(d) at least one sweetener and optionally at least one flavoring agent having the capability of masking the disgusting flavor of lysine,

(e) and a pharmaceutically or dietetically acceptable carrier.

This invention also relates to a process for preparing the tablets according to this invention, which consists in the mixing or conjunction of the active ingredients (a), (b) and (c) with the taste masking agent (d) and with one or several carriers (e) such as diluents, excipients, sticking agents, buffering agents, bulk agents, and/or lubricating agents, to realize a pharmaceutical form suitable to be suckled or chewed, such as tablets, or lozenges. This production is obtained according to the known methods of the pharmacotechny.

The following examples are merely illustrative of the invention without limiting it in any manner.

EXAMPLE I

Tablets to be sucked

Component	Function	Declared amount/tablet [mg]
Active Ingredients (a) + (c)		
(L)-lysine monohydrochloride	essential amino acid	50.00
Betatab, 10 % (E160a)	vitamin	5.14 (0.514 β-Carotin)
Vitamin A palmitate (500000 IU/g)	vitamin	1.43 (715 IU)
Vitamin B1 nitrate (thiamine mononitrate rocoat 33.3 %)	vitamin	1.50 (0.50 Vit. B1 nitrate)
Vitamin B2 (Riboflavin rocoat 33.3 %)	vitamin	1.65 (0.55 Vit. B2)
Vitamin B6 hydrochloride (Pyridoxin hydrochloride rocoat 33.3 %)	vitamin	1.65 (0.55 Vit. B6 hydrochloride)
Vitamin B12 (Cyanocobolamine 0.1 %)	vitamin	0.60 (0.60 10^{-3} Vit. B12)
Vitamin C (Ascorbic acid 90 %)	vitamin	24.44 (22.0 Vit. C)
Vitamin D3 (Cholecalciferol 100.000 IU/g)	vitamin	1.50 (150 IU Vit. D3)
Vitamin E acetate (50 % d,l-α-tocopherol acetate)	vitamin	10.43 (5.215 Vit. E acetate)
Folic acid	vitamin	0.05
Biotin	vitamin	1.50 10^{-3}(15.0 10^{-3} Vit. H)
Vitamin PP (Nicotinamide rocoat 33,3 %)	vitamin	18.0 (6.0 Vit. PP)
Minerals (b)		
Copper carbonate	mineral	0.52
Dicalcium phosphate anhydrous	mineral	220.64
Ferrous (II) fumarate (coated 60 %)	mineral	12.68
Zinc oxide (coated 50 %)	mineral	6.25
Magnesium oxide, heavy	mineral	19.89

Taste mask (d)		
Aspartame powder	sweetener	6.00
Natural Orange Flavor	flavor	22.00
Dextrose	sweetener	275.00
Prosweet®	flavor	4.00
Sorbitol	sweetener/carrier	597.44
Carrier (e)		
Citric acid	acidifier	50.00
Silicon dioxide, colloidal	binder	14.00
Magnesium stearate	lubricant	12.00
Hydrogenated vegetable oil	diluent	25.00

Once the mixture of components (a), (b), (c) and (d) are perfectly homogenized, the carriers (e) are added thereto. The resulting powder is screened then tabletted by direct compression into tablets having a diameter of 16.0 mm, a thickness of 6.5 to 7.5 mm, a mean weight of about 1400 mg and a hardness of not more than 200 N.

These tablets show a good geometric stability. They swell into an expanded form, practically equal to that of the starting tablet. They progressively and completely release the active ingredients when in contact with saliva in the mouth.

EXAMPLE II

Determination of the acceptability of the tablets according to this invention.

The acceptability is determined on a group of 144 healthy children (age 6 to 14 years) which received a tablet which corresponds to the recipe of example 1 containing 50 mg (L)-lysine hydrochloride. Each child chewed this tablet until it has been completely consumed. The children are subsequently interviewed about the taste of the product. The same test is then repeated using different multi-vitamin preparations (Prep A and Prep B) presently on the market which do not contain lysine at all.

The following results are obtained:

	Example 1 (%)	Prep A (%)	Prep B (%)
Observation of behaviour:			
calmly chews the tablet, it seems to taste well	52	63	36
Likeability of the taste:			
very good taste	33	45	18
good taste	28	23	26
Sweetness of tablets:			
sweet enough, just right	70	76	68
Sourness of tablets:			
too sour	29	18	39
not too sour	71	82	61
Feeling in the mouth after chewing:			
good	76	80	58
not so good	24	20	42
Interest in eating again:			
very interested	20	32	11
quite interested	49	35	35

These results clearly show that the tablets according to the present invention despite the high content of (L)-lysine are in the same range of acceptability as Prep A, but are much more acceptable than Prep B.

CLAIMS:

1. A tablet with enhanced compliance by humans comprising the following constituents:

(a) at least one vitamin,

(b) at least one mineral which is manganese (II) gluconate, copper (II) carbonate, calcium phosphate, ferrous (II) fumarate, zinc oxide or magnesium oxide,

(c) lysine or a pharmaceutically acceptable salt thereof,

(d) at least one sweetener and optionally at least one flavoring agent having the capability of masking the disgusting flavor of lysine,

(e) and a pharmaceutically or dietetically acceptable carrier,

wherein said tablet is obtainable by mixing of the different components (a) to (e) and tabletting by direct compression.

2. A tablet according to claim 1, wherein group (a) comprises at least one vitamin which is β-carotene, vitamin A palmitate, vitamin B1 nitrate, vitamin B2, vitamin B6 hydrochloride, vitamin B12, vitamin C, vitamin D3, vitamin E acetate, folic acid, vitamin H or vitamin PP.

3. A tablet according to claim 1 or 2, wherein group (a) is a mixture of vitamins consisting essentially of 0.4 to 0.8 mg of β-carotene, 500-1500 IU of vitamin A palmitate, 0.3 to 1.0 mg of vitamin B1 nitrate, 0.3 to 1.0 mg of vitamin B2, 0.3 to 1.0 mg of vitamin B6 hydrochloride, 0.4 to 1.0 µg of vitamin B12, 15 to 40 mg of vitamin C, 100-300 IU of vitamin D3, 3.0 to 9.5 mg of vitamin E acetate, 20 to 80 µg of folic acid, 10 to 25 µg of vitamin H and 4 to 10 mg of vitamin PP per unit dosage.

4. A tablet according to any one of claims 1 to 3, wherein group (b) is a mixture consisting essentially of 0.2 to 0.8 mg of copper (II) carbonate, 150 to 300

mg of dicalcium phosphate anhydrous, 8.0 to 20 mg of ferrous (II) fumarate, 4 to 9 mg of zinc oxide and 12 to 28 mg of magnesium oxide per unit dosage.

5. A tablet according to any one of claims 1 to 4, wherein group (c) comprises (L)-lysine monohydrochloride.

6. A tablet according to any one of claims 1 to 5, wherein group (c) consists essentially of 10 to 100 mg of (L)-lysine monohydrochloride per unit dosage.

7. A tablet according to any one of claims 1 to 6, wherein group (d) comprises at least one sweetener which is calcium saccharinate, ammonium cyclamate, ammonium glycirhizinate, Aspartame, glucose or glucitol, and at least one flavouring agent which is natural citrus flavor, natural orange flavor or Prosweet®.

8. A tablet according to claim 7, wherein the glucitol is the tablet according to any one of claims 1 to 6, wherein group (d) comprises at least one sweetener which is calcium saccharinate, ammonium cyclamate, ammonium glycirhizinate, Aspartame, glucose or glucitol, and at least one flavouring agent which is natural citrus flavor, natural orange flavor or Prosweet®.

9. A tablet according to any one of claims 1 to 8, wherein group (d) consists essentially of 1.0 to 10.0 mg of Aspartame®, 5.0 to 50.0 mg of glucose syrup, 200 to 800 mg of sorbitol, 5.0 to 50.0 mg of natural orange flavor and 1.0 to 10.0 mg of Prosweet® per unit dosage.

10. A tablet according to any one of claims 1 to 9, wherein group (e) comprises at least one carrier which is a diluent, an excipient, a sticking agent, a buffering agent, a bulk agent, a lubricating agent or a colorant.

11. A tablet according to any one of claims 1 to 10, which can be chewed or sucked with enhanced compliance by children and/or juveniles comprising the following constituents:

(a) a mixture of vitamins consisting essentially of 0.4 to 0.8 mg of β-carotene, 500-1500 IU of vitamin A palmitate, 0.3 to 1.0 mg of vitamin B1 nitrate,

0.3 to 1.0 mg of vitamin B2, 0.3 to 1.0 mg of vitamin B6 hydrochloride, 0.4 to 1.0 µg of vitamin B12, 15 to 40 mg of vitamin C, 100-300 IU of vitamin D3, 3.0 to 9.5 mg of vitamin E acetate, 20 to 80 µg of folic acid, 10 to 25 µg of vitamin H and 4 to 10 mg of vitamin PP per unit dosage,

(b) a mixture of minerals consisting essentially of 0.2 to 0.8 mg of copper (II) carbonate, 150 to 300 mg of dicalcium phosphate anhydrous, 8.0 to 20 mg of ferrous (II) fumarate, 4 to 9 mg of zinc oxide and 12 to 28 mg of magnesium oxide per unit dosage,

(c) 10 to 100 mg of (L)-lysine monohydrochloride per unit dosage,

(d) a mixture of sweeteners and flavoring agents consisting essentially of 1.0 to 10.0 mg of Aspartame, 5.0 to 50.0 mg of glucose syrup, 200 to 800 mg of sorbitol, 5.0 to 50.0 mg of natural orange flavor and 1.0 to 10.0 mg of Prosweet® per unit dosage;

(e) a pharmaceutically or dietetically acceptable carrier,

wherein the complete dosage unit weighs 500 to 2000 mg.

12. Use of a tablet as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, for the preparation of a nutritional supplement for improving the physiological state of humans.

13. Use of a tablet as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, for the preparation of a nutritional supplement for improving the development and growth of children and/or juveniles.

14. A tablet as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, for improving the physiological state of humans.

15. A tablet as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, for improving the development and growth of children and/or juveniles.